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The peripheral–central chemoreflex interaction: where do we stand and what is the next step?

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It has been known for more than a century that two distinct set of chemosensitive mechanisms contribute to human ventilatory control. This tightly controlled chemoreflex system operate via a negative feedback loop, mediating cardiorespiratory responses, which maintains arterial blood gases and acid–base balance within normal limits in a healthy organism under most circumstances. In contrast, dysfunctional chemoreflex sensitivity contributes to abnormal ventilatory control, turning this mechanism into a key point in the pathophysiology of highly prevalent diseases, like chronic heart failure (CHF), hypertension, chronic obstructive pulmonary disease (COPD), and obstructive sleep apnoea (OSA) (Kara *et al.* 2003).

Peripherally, the chemoreflex control of ventilation is mediated by polymodal receptors (mainly in the carotid body; CB), which are sensitive to changes in the concentration of various substances in the arterial blood, such as carbon dioxide (CO_2), hydrogen ions (H^+), lactate, potassium, glucose, insulin and angiotensin. However, the major stimulus to peripheral chemoreceptors is the reduction in partial pressure of oxygen in the arterial blood (P_{aO_2}). Centrally, receptors are located in many brainstem areas, including the nucleus of the solitary tract (NTS), raphe, locus coeruleus and cerebellar fastigial nucleus. But, more recently, evidence from Guyenet *et al.* (2010) and Stornetta *et al.* (2006) (cited by Dempsey & Smith, 2014) has emphasized that the retrotrapezoid nucleus (RTN), which is characterized by glutamatergic interneurons expressing Phox2b, is the major potential site of central CO_2/H^+ chemoresponsiveness.

Despite the existence of separate chemosensitive areas, with different stimulus characteristics, peripheral and central chemoreflexes do not act independently of each other. The discovery of important sites of convergence between CB and brainstem chemoreceptors in the NTS and RTN supports the idea of peripheral–central chemoreflex interdependence (Stornetta *et al.* 2006; cited by Dempsey & Smith, 2014). However, how these receptors interact to provide coordinated control of ventilation remains controversial. Previous studies provided evidence of different forms of peripheral–central interaction, i.e. (1) hypoadditive, where the stimulation of one reflex attenuate the response of the other, (2) additive, where both reflexes do not interact in a significant way, or (3) hyperadditive, where the stimulation of one reflex results in increased response of the other (also known as synergism). The controversy over the nature of this interaction has been attributed to heterogeneous protocols, preparations and species involved in previous studies. For example, some of these studies included decerebrated, vagotomized and anaesthetized animals (Day & Wilson, 2009), which is a highly controlled preparation, but could *per se* reduce the ventilatory response in face of central and/or peripheral stimulation or inhibition. Consequently, it may not reflect the real ventilatory control of an intact awake animal or human. Others investigated the interaction in humans, via non-invasive studies, which is limited to interpreting the function of each reflex separately.

Based on the unclear nature of the chemoreflexes interaction, Smith *et al.* (2015) published a recent study in *The Journal of Physiology* using an intricate invasive preparation in intact, non-anaesthetized, awake dogs, which allowed independent peripheral and central stimulation or inhibition. The left CB was denervated and the right carotid sinus was prepared with a vascular occluder and catheter allowing reversible isolation and extracorporeal perfusion of the intact CB. Then, the intact CB was exposed to three different conditions: (1) normal stimuli to the CB, with pH, P_{aO_2} and P_{aCO_2} concentrations matching a given dog's eupnoeic values; (2) CB inhibition with hypocapnic normoxic blood; and (3) CB stimulation with hypercapnic normoxic blood. In the steady-state of each CB perfusion, fractional inspired CO_2 (F_{ICO_2}) was progressively increased to stimulate central chemoreceptors and changes in ventilation, diaphragm electromyography (EMG), blood gases and arterial pressure were quantified.

The main finding of Smith *et al.* (2015) was that the increase in the slope of minute ventilation and inspiratory flow rate *vs.* changes in central P_{CO_2} was 2- to 4-fold greater when the isolated CB was exposed to hypercapnia *vs.* hypocapnia, and ~2-fold greater during normocapnia *vs.* hypocania. Thus, specific CB stimulation or inhibition by hypercapnia/hypocapnia, while central chemoreceptors were stimulated by increased F_{ICO_2}, resulted in hyperadditive interaction. Noteworthy, the present findings corroborate those previously reported by Dr Dempsey's lab (Blain *et al.* 2010) using the same dog preparation. Earlier, authors demonstrated that inhibition or stimulation of vascularly isolated CB with changes in O_2 levels also affected the magnitude of the ventilatory response to central hypercapnia in a hyperadditive fashion. Therefore, based on current and previous findings, Smith *et al.* (2015) suggest that changes in P_{O_2} and P_{CO_2} at the CB have similar effects on peripheral–central interaction for the control of ventilation.

Results reported by Smith *et al.* (2015) are unique, since they were obtained in intact, unanaesthesized, awake animals, which is probably the best method used so far to translate results to spontaneously breathing humans. Nevertheless, they should be interpreted in light of some limitations. One is the use of systemic hypercapnia, which may not only stimulate central chemoreceptors, but may directly modify the activity of other receptors, such as pulmonary stretch receptors, or even the activity of neurons from the 'central respiratory controller', where supposedly all inputs that regulate ventilation are integrated. Unfortunately, it is impossible to exclusively manipulate the central chemoreceptors in intact, unanaesthesized and awake animals without systemic effects. To avoid systemic effects, Day & Wilson (2009), for example,

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have proposed a rat model that allows independent perfusion of brainstem and peripheral chemoreceptors. However, this preparation has low applicability to humans and its results have not been consistent with others (Blain *et al.* 2010; Smith *et al.* 2015). In addition, both Smith *et al.* (2015) and Blain *et al.* (2010) reported hyperadditive effects, but more ventilatory variables were affected by changes in CB P_{O_2} (i.e. minute ventilation, tidal volume, breathing frequency and diaphragm EMG) than CB P_{CO_2} (i.e. minute ventilation and inspiratory flow rate). The preparation in both studies was similar, but dogs were not the same, which raises the following questions: is peripheral–central chemoreflex synergism more dependent on the O_2 level at the CB than the CO_2 level? This is plausible, since the CB seems to be more responsive to hypoxia than hypercapnia. However, this complex question requires further investigation and possible differences in operating ranges of the CB for P_{O_2} and P_{CO_2} should be considered. Alternatively, are the quantitative differences between Smith *et al.* (2015) and Blain *et al.* (2010) only attributed to data variability? These questions could be answered by manipulating CO_2 and O_2 using the same dogs in a single study.

Even with the aforementioned limitations, results from Smith *et al.* (2015) and Blain *et al.* (2010) were consistent with some previous studies that used different models/species. For instance, dogs, goats, ponies and humans show hypoventilation at rest and reduced responsiveness to systemic normoxic or hyperoxic hypercapnia within few days after bilateral CB denervation. Altogether, these findings support the hyperadditive interaction. Then, assuming that the interaction is indeed hyperadditive, many interesting questions arise whose answers may further confirm the nature of the interaction and widen its practical application to human physiology and pathophysiology. For example, the existing literature supports that peripheral chemoreceptors are sensitized during exercise (Stickland *et al.* 2007; cited by Dempsey & Smith, 2014). Thus, is the interaction even more hyperadditive during exercise than rest? Furthermore, results reported by Smith *et al.* (2015) and Blain *et al.* (2010) were obtained via acute changes in regional and/or systemic levels of O_2 and CO_2 in healthy animals. Then, how does the peripheral–central chemoreflex interaction work for the control of ventilation in animals/humans with chronic hypercapnia/hypoxaemia? This is a complex issue, which probably depends on the underlying disease. For example, it is well established that both central and peripheral chemoreflex sensitivity is augmented in CHF and OSA, which contributes to ventilatory and autonomic abnormalities (Kara *et al.* 2003). Accordingly, it would be relevant to know if the peripheral–central chemoreceptors exhibit a similar synergism to that observed in healthy dogs and how this evolved during the natural history of these diseases. Patients with advanced COPD, in turn, commonly show chronic hypercapnia and may have blunted central CO_2 sensitivity. Thus, is the peripheral–central chemoreflex interaction attenuated in these patients with COPD? Even more complex, but also scientifically exciting, is dissecting the peripheral–central chemoreflex interaction in patients with overlapping diseases, such as CHF and COPD. Such a condition is relatively frequent and leads to catastrophic symptoms, quality of life and prognosis.

In conclusion, Smith *et al.* (2015) demonstrated that central chemoreceptor sensitivity to hypercapnia in non-anaesthetized intact dogs is dependent on CB afferent activity, leading to hyperadditive peripheral–central interaction for the control of ventilation. So what comes next? Future studies should keep looking at this physiological phenomenon under an integrative perspective, to advance knowledge about its contribution to cardiorespiratory control in health and disease, under varied physiological states, including rest, exercise and sleep. Hopefully, this will culminate with treatments that can hit involved mechanisms right on target to prevent or alleviate cardiorespiratory diseases.

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Additional information

Competing interests

None declared.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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